

Figure 1



1

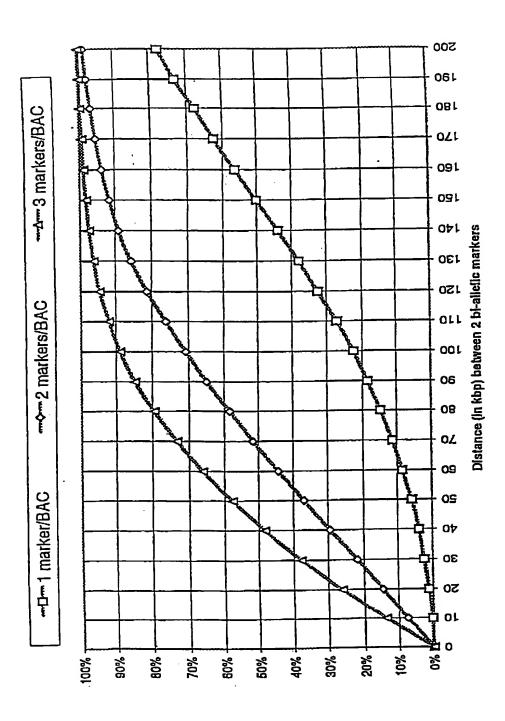
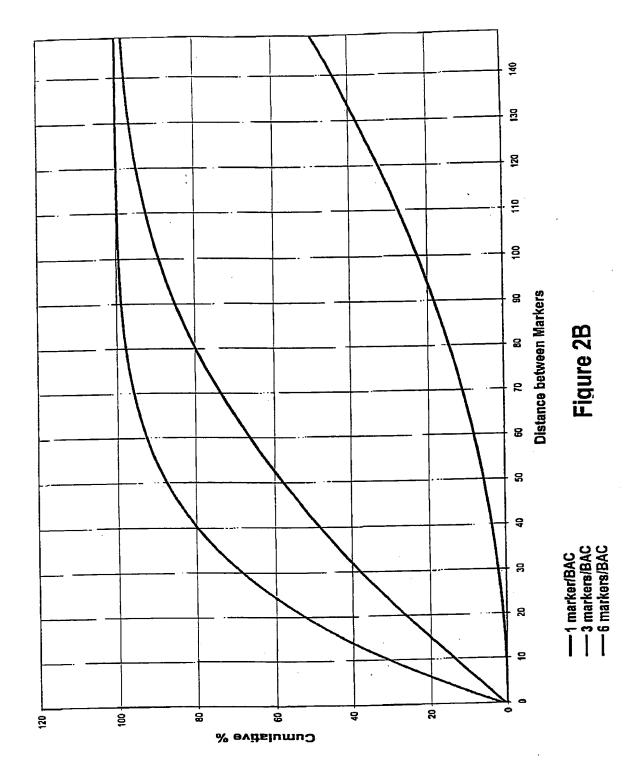


Figure 2A

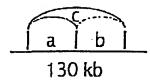






### LD in a random French caucasian population

- 54 sized « random » BACs covering 8100 kb
- 213 SNP; 2 to 6 / BAC, mean allele frequency = 0.3
- Order and distance unknown
- For 1 BAC:



- \*  $\overline{m}$  intermarker distance : 130/3 = 43 kb
- \*  $\overline{m}$  LD strength estimate: m (a,b,c) = 0.51
- For 54 BACs:
- \* m intermarker distance = 38 kb
- \*  $\overline{m}$  LD strength estimate =  $0.63 \pm 0.05$  (324 pairs)
- For 19 unlinked SNPs: m LD strength estimate =  $0.12 \pm 0.007$  (171 pairs)



### p-VALUE DISTRIBUTION

-							
#aff	150						
# non aff	150						
	pAi non aff	0	1,0	0,2	0,3	0,4	0,5
ΔpAi	0,05	8,77E-05	0,05 8,77E-05 0,06407752 0,14252002 0,19106311 0,21543442 0,22009395	0,14252002	0,19106311	0,21543442	0,22009395
∆ pAi	0,1	1,91E-08	1,91E-08 0,00060364	0,00467774 0,01023571 0,01382303 0,01382303	0,01023571	0,01382303	0,01382303
Δ pAi	0,15	3,06E-12	3,06E-12 1,3319E-06 3,8827E-05	3,8827E-05	0,0001478	0,0001478 0,0002343 0,00020218	0,00020218
Δ pAi	0,2	3,22E-18	3,22E-16 9,1413E-10	9,0305E-08	5,733E-07	5,733E-07 9,6336E-07	5,733E-07
A DAi	0,25	2,08E-20	2,08E-20 2,2614E-13 6,2679E-11	6,2679E-11	5,873E-10	5,873E-10 8,7113E-10 2,5396E-10	2,5396E-10
∆ pAi	0,3	0,3 7,82E-25	2,152E-17	1,3261E-14 1,5189E-13 1,5189E-13	1,5189E-13	1,5189E-13	1,3261E-14
ΔpAi	0,35	1,62E-29	7,9823E-22 8,4152E-19 9,1669E-18 4,2713E-18 5,5844E-20	8,4152E-19	9,1669E-18	4,2713E-18	5,5844E-20
∆ pAi	0,4	1,73E-34	0,4 1,73E-34 1,1282E-26	l	1,524E-23 1,1488E-22	1,524E-23 1	1,1282E-26

# att	200						
# non aff	200						
	pAi non aff	0	0,1	0,2	6,0	0,4	0,5
ΔpAi	0,05	5,92E-06	0,03250945	0,09039173	0,13111935	0,15260313	0,15678006
ΔρΑi	0.1	8,65E-11	7,4765E-05	0,00109084	0,00302686	0,00447365	0,00447365
ΔpAi	0,15	8,02E-16	2,3653E-08	2,0257E-06	1,1771E-05	2,1573E-05	1,7772E-05
∆ pAi	0.2	4,18E-21	1,5375E-12	6,7374E-10	7,764E-09	1,5417E-08	7,764E-09
A DAI	0.25	1,13E-28	2,525E-17	4,4025E-14	8,5532E-13	1,4423E-12	2,8149E-13
A DA	0.3	1.47E-32	1.1488E-22	5,8424E-19	1,4886E-17	1,4886E-17	5,8424E-19
A DAi	0.35	100	1,4784E-28	1,5457E-24	3,6958E-23	1,3394E-23	4,197E-26
Δ pAi	0,4		5,2308E-35	7,6438E-31	ŀ	1,1224E-29 7,6438E-31	5,2308E-35

aff affected individuals

# non aff non affected individuals

pAi non aff allele frequency in non affected individuals

A pAi % Difference in allele frequency between affected and non-affected individuals

Figure 3 (I)

09858289.032003



### DISTRIBUTION p-VALUE

200

#aff

# non aff	200						
	pAi non aff	0	1,0	0,2	0,3	4'0	0,5
∆ pAi	0,05	8E-13	0,00072323	0,00741965	0,0169842	0,02371865	0,02516449
∆ pAi	0,1	1,07E-24	3,7948E-10	2,4176E-07	2,7579E-06	6,9679E-06	6,9679E-06
∆ pAi	0,15	3,81E-37	1,0719E-18	5,8344E-14	4,2622E-12	1,8601E-11	1,1611E-11
∆ pAi	0,2	2,96E-50	5,0895E-29	1,6881E-22	6,9321E-20	3,7441E-19	6,9321E-20
ΔpAi	0,25	4,27E-64	7,2043E-41	7,7528E-33	1,194E-29	4,3462E-29	7,6438E-31
ΔpAi	0,3	9,7E-79	3,9328E-54	6,3017E-45	1,9429E-41	1,9429E-41	6,3017E-45
∆ pAi	0,35	2,91E-94	8,8513E-69	8,7879E-59	2,3478E-55	1,8839E-56	1,1206E-62
∆ pAi	0,4	9,5E-111	7,7199E-85	1,8063E-74	1,4484E-71	1,8063E-74	7,7199E-85

#aff	150						-
# non aff	850						
	pAi non aff	0	0,1	0,2	0,3	0,4	0,5
∆ pAi	0,05	2,16E-20	0,00994614	0,04896055 0,08358651	0,08358651	0,10417953	0,11025423
ΔpAi	0,1	2,01E-39	5,571E-07	0,00010149 0,00058665 0,00119145	29982000'0	0,00119145	0,00139743
Δ pAi	0,15	1,11E-58	2,7555E-13	8,462E-09	8,462E-09 2,9851E-07	1,2395E-06	1,6229E-06
ΔρΑi	0,2	3,27E-78	2,1683E-21	3,2211E-14	1,1049E-11	1,111E-10	1,5638E-10
ΔpAi	0.25	4,96E-98	4,4952E-31	6,5226E-21	3,1015E-17	3,1015E-17 2,5169E-16	1,1763E-15
ΔDAi	0,3	3,7E-118	3,6987E-42		6,9335E-24	8,129E-29 6,9335E-24 5,4331E-22	6,5857E-22
∆ oAi	0,35	1,4E-138	1,6797E-54	7,1058E-38	1,2938E-31	2,8415E-29	2,5869E-29
∆ pAi	0,4	0,4 2,4E-159	5,4915E-68	4,8846E-48	4,8846E-48 2,1003E-40 1	1,3332E-37	6,8178E-38

non affected individuals affected individuals # non aff #aff

pAi non aff

allele frequency in non affected individuals % Difference in allele frequency between affected and non-affected individuals



p-VALUE DISTRIBUTION

#aff	200						
# non aff	200		,				
	pAi non aff	0	0,1	0,2	0,3	0,4	0,5
∆ pAi	90'0	1,08E-12	0,00789803	0,03942584 0,06867566	0,06867566	0,08621572	0,09083704
Δ pAi	0,1	3,45E-24	4,4217E-07		5,6883E-05 0,00031976	0,0006363	0,00070881
Δ pAi	0,15	5,9E-36	4,3025E-13		3,3635E-09 9,2134E-08	3,319E-07	3,5871E-07
∆ pAi	0,2	4,73E-48	1,5566E-20	1,0346E-14	1,7218E-12	1,1512E-11	- 1,0047E-11
∆ pAi	0,25	1,67E-60	3,5436E-29	1	2,0473E-21 2,2178E-18	1,1498E-17	1,3524E-17
∆ pAi	6,0	2,46E-73	7,2498E-39		2,0601E-25	3,0748E-29 2,0601E-25 3,4525E-24	7,4807E-25
Δ pAl	0,35	1,44E-86	1,6945E-49	3,9559E-38	1,4118E-33	2,662E-32	1,4118E-33
∆ pAi	4,0	3,2E-100	3,2E-100 5,3051E-81		7,1282E-43	4,7325E-48 7,1282E-43 1,0691E-41 7,2652E-44	7,2652E-44

#aff	200						
# non aff	1000						
	pAi non aff	0	0,1	0,2	6,0	0,4	0,5
Δ pAi	90'0	6,48E-24	5,7827E-05	0,00172627	0,00551541	0,00882876	0,00978249
Δ pAi	0,1	6,53E-47	3,065E-14	1,0301E-09	4,3205E-08	1,8833E-07	2,2731E-07
ΔpAi	0,15	1,2E-70	2,0716E-27	3,7441E-19	"	4,6626E-16 6,9719E-15	6,9719E-15
∆ pAi	0,2	3,33E-95	1,1636E-43	1,6614E-31	8,5632E-27	4,1421E-25	1,9885E-25
∆ pAi	0,25	1,2E-120	1,7683E-62	1,5329E-46	3,1722E-40	8,6765E-39	3,6071E-39
∆ pAi	6,0	5,3E-147	1,526E-83	4,2697E-64	2,5968E-56	3,9328E-54	2,5968E-56
∆ pAi	0,35	2,4E-174	1,184E-108	4,5658E-84	4,7426E-75	4,2624E-73	4,0958E-77
∆ pAi	0,4	9,4E-203	1,082E-131	2,137E-106	1,8014E-96	1,8014E-96 3,3252E-95	6,725E-102

affected individuals #aff

non affected individuals # non aff

pAi non aff Δ pAi

allele frequency in non affected Individuals % Difference in allele frequency between affected and non-affected individuals

Figure 3 (III)





ALLELIC ASSOCIATION 3,000 MARKERS MAP

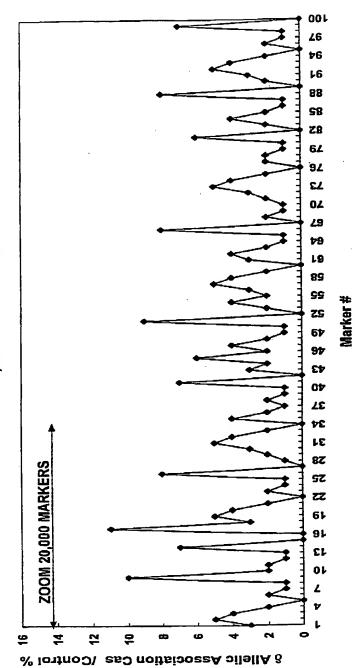


Figure 4



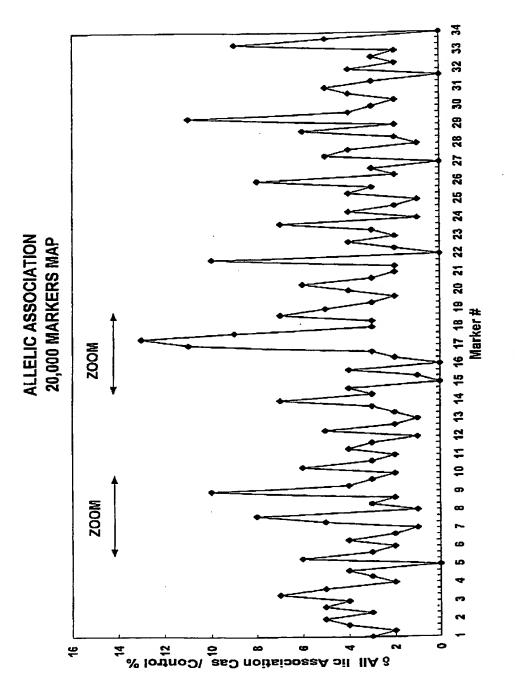


Figure 5



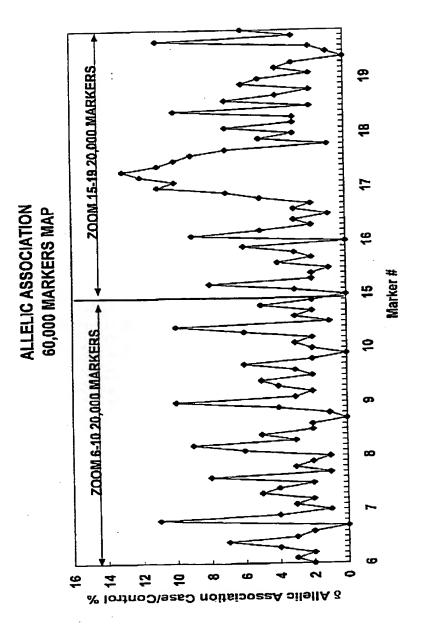


Figure 6



### APO E REGION HAPLOTYPE FREQUENCY ANALYSIS

AD CONTROLS (248)	
POPULATIONS	

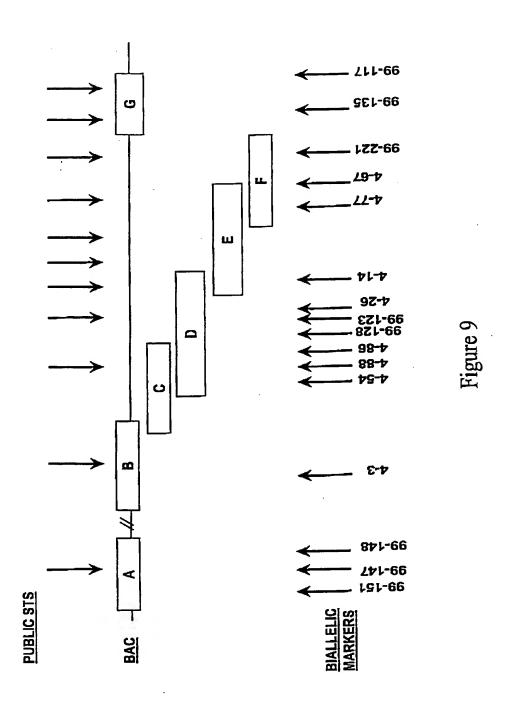
markers	99-366	99-344	99-359	99-355	haplotype i	haplotype frequencies	-sppo	P value
p value	3,01E-01	1,11E-01	6,63E-01	1,38E-01	seseo	controls	ratio	
haplotype 1	ပ	ပ			0,404	806,0	1,52	3,05E-03 ***
haplotype 2			∢		0,203	0,165	1,29	1,24E-01 *
haplotype 3			G	တ	0,375	906,0	1,36	2,83E-02 **
haplotype 4	ပ		∢		0,264	0,209	1,36	5,95E-02 **
haplotype 5		Ø		∢	0,116	0,071	1,70	1,64E-02 **
haplotype 6	ပ			∢	0,15	0,129	1,19	3,59E-01
haplotype 7	<b>}</b>		O	ŋ	0,225	0,122	2,09	4,76E-05 ****
haplotype 8	<b>-</b>	⋖	တ	G	0,228	0,108	2,44	2,05E-08 *****

Figure 7



APO E REGION HAPLOTYPE SIMULATION POPULATION: 225 CASES vs 248 CONTROLS







# PROSTATE CANCER ASSOCIATION STUDIES (FIRST SCREENING)

PROSTATE CANCER NON AFFECTED	e CASES = 112 CONTROLS=76	7 35 sporadic cases > 65 years	ics + 77 familial cases PSA<4
Population	Sample size	Population	Characteristics

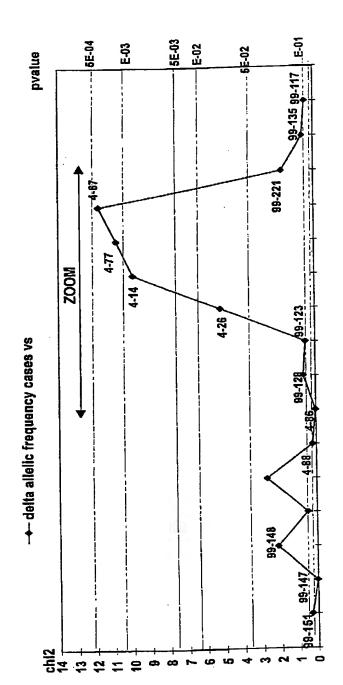
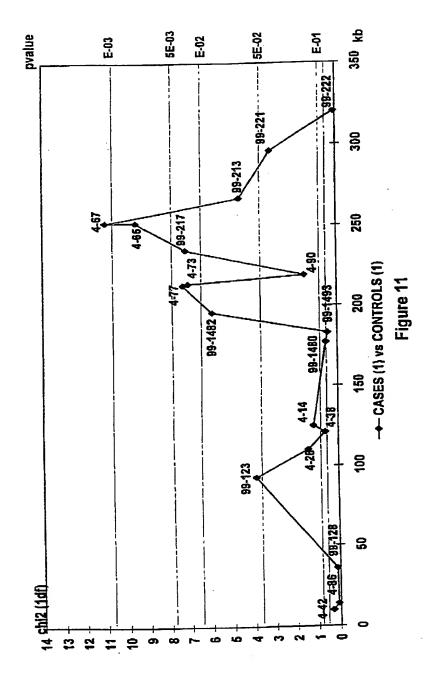


Figure 10



## PROSTATE CANCER ASSOCIATION STUDIES (ZOOM)

	PROSTATE CANCER	NON-AFFECTED
	CASES (185)	CONTROLS (104)
characteristics	47 sporadic cases	> 65 years
of populations	+ 138 familial cases	PSA<4





### PROSTATE CANCER HAPLOTYPE FREQUENCY ANALYSIS

	PROSTATE CANCER	NON-AFFECTED
	CASES (281)	CONTROLS (130)
characteristics	143 sporadic cases	> 65 years
of populations	+ 138 familial cases	PSA<4

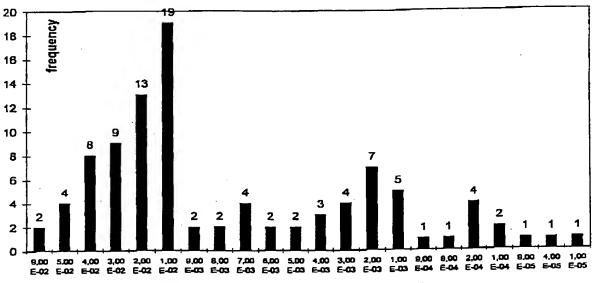
markera	89-123	4.26	4-14	4.77	99-217	4.67	99-213	99-221	99-135	hapk	haplotype		
bacs	H0287B09	8018	B0189E08			B0463F01			B0725B12	fredu	frequencies	relative	pvalue
Ranga						1	_					risk	
Billey	2 nnF.01   1.00E-01   1.00E-	1 00E-01	1.00E-01	2.00E-02	01   2.00E-02   2.00E-02	6,00E-04	9,00E-02 7,00E-01 2,00E-01	7,00E-01	2,00E-01	Cases	controls		
P value		۵	C	] [	-	<u> </u>	ပ	⋖	A	0,075	0,018	4,42	9,00E-04 ***
Alaboty o adyloidan	>	( ⊲	) C	) C		۰ ۱	ပ	∢	∀	0,095	0,016	6,46	6,00E-05 ***
napiotype / 200kb		( ⊲	י כ	) ლ	۰ ۱–	· <b>i</b> —	ပ	<		0,116	0,019	6,78	1,00E-05 ****
naplotype o < 100km		c	o c		- 1-		ပ	<		0,117	0,013	10,06	9,00E-07 *****
naplotype 3 < 17 IND			)	<b>.</b> C			ပ	∢		0,117	0,025	5,17	2,00E-05 ****
hapiotype 4 < 53Kuz				)	. J-	· <b>-</b>	ပ	<<		0,117	0,027	4,78	2,00E-05 ****
hapiotype 3.1 <54Kb>				ď		· }—	ပ	•		0,222	0,109	2,33	4,00E-05 ****
napiotype 3.2 <34kb>	-			) C	-					0,251	0,134	2,17	2,00E-04 ****
haptotype 2.2 <38KD				)	. <b>}-</b>	· <b> -</b>	ပ			0,226	0,112	2,32	1,00E-04 ***
haplotype Z <32kp>					- 1					0,256	0,148	2,01	3,00E-04 ***
haplotype 1.1 <17 Kb2					-	. 1-	ပ			0,233	0,129	2,05	6,00E-04 ***
haplotype 1.2 <15 KD>													

Figure 12



### PROSTATE CANCER HAPLOTYPE SIMULATIONS (100 ITERATIONS)

								haplotype f	requencies	relative	pvalue	ĺ
m	arkers	4-14	4-77	99-217	4-67	99-213	99-221	cases	controls	risk		
ha	plotype	С	G	T	T	G	Α	0,117	0,013	10,06	9,00E-07	ĺ



pvalue max of haplotypes for 100 simulations

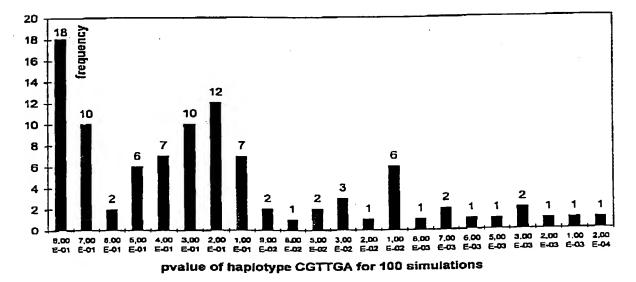


Figure 13



### AVERAGE LD PATTERN GENOMIC HETEROGENEITY

Recombination rate	Lower	Higher
	Α	В
Nb markers	89	69
All SNP	0.61	0.42
	(749)	(1190)
Rare < 0.2	0.75	0.17
Rare vs rare	(65)	(158)
Frequent > 0.2	0.51	0.49
Frequent vs frequent	(410)	(544)
Rare vs frequent	0.72	0.41
	(274)	(488)

FIGURE 14

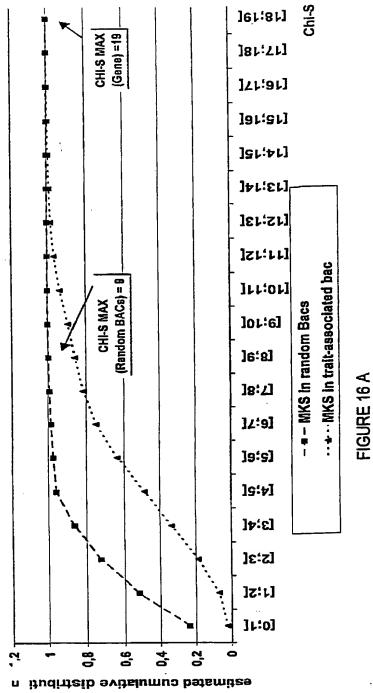


### Exonic/nonexonic LD

	Nb pairs	Average intermarker distance	Average LD
Exonic SNPs	36	26 kb	0.65±0.021
Non exonic SNPs	60	36 kb	0.48±0.018
Exonic/Non exonic	96	32 kb	0.60±0.015

FIGURE 15







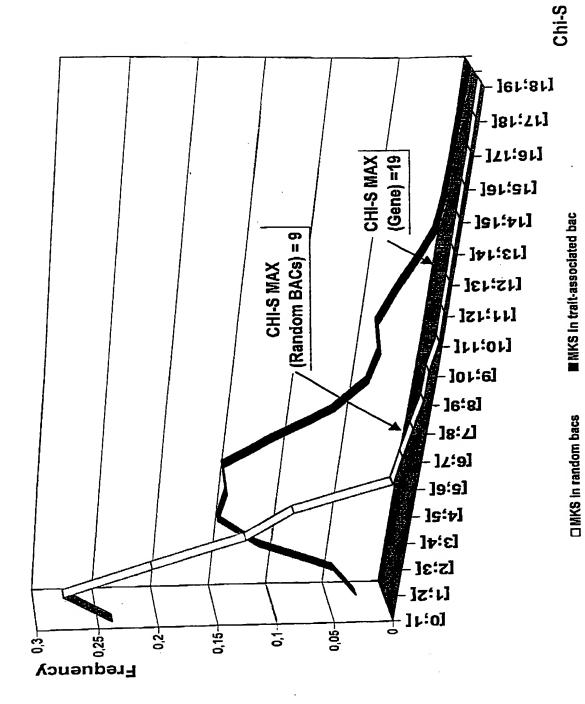
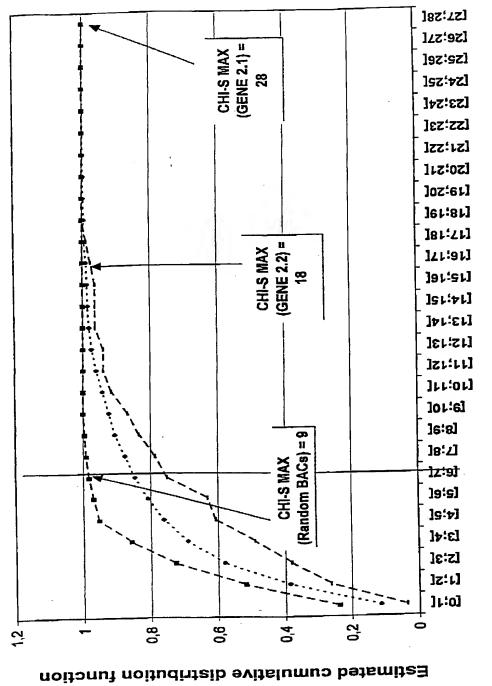


FIGURE 16B





- • - MKS in random BACs ···•·· MKS in BAC of GENE 2 (1:all mks) - - - - MKS in BAC of GENE 2 (2: mks not desequilibrium)

FIGURE 17A



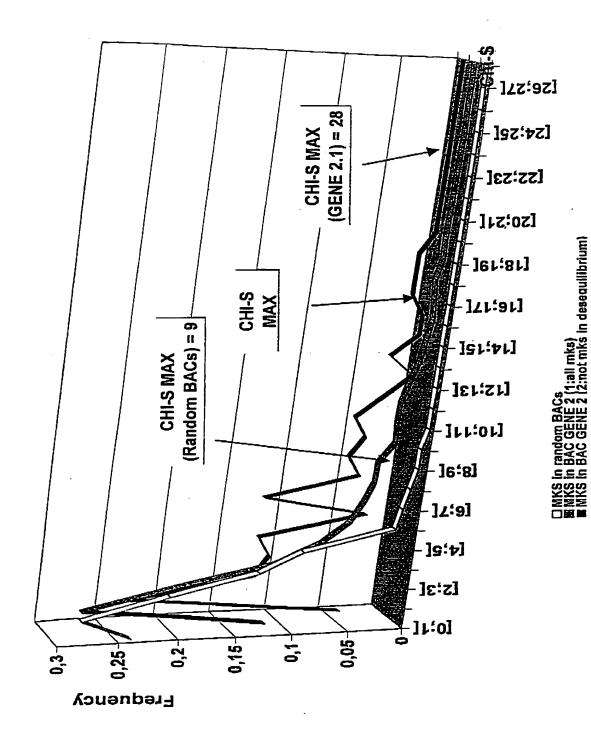
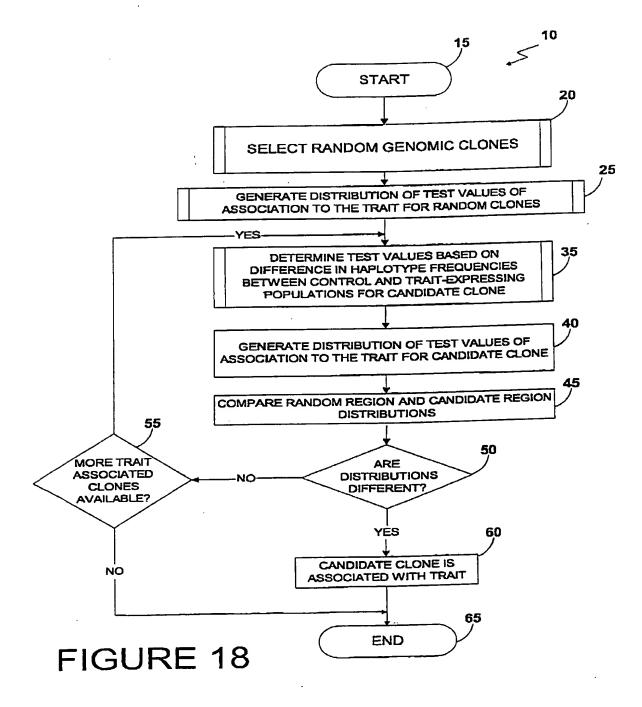
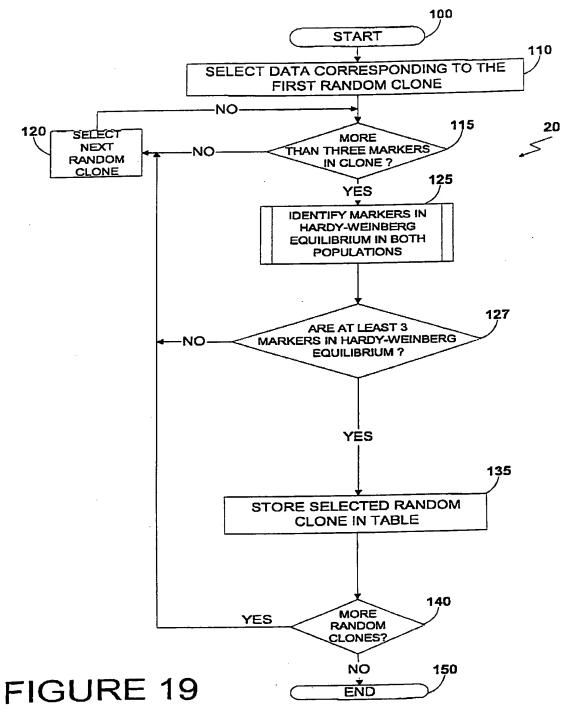


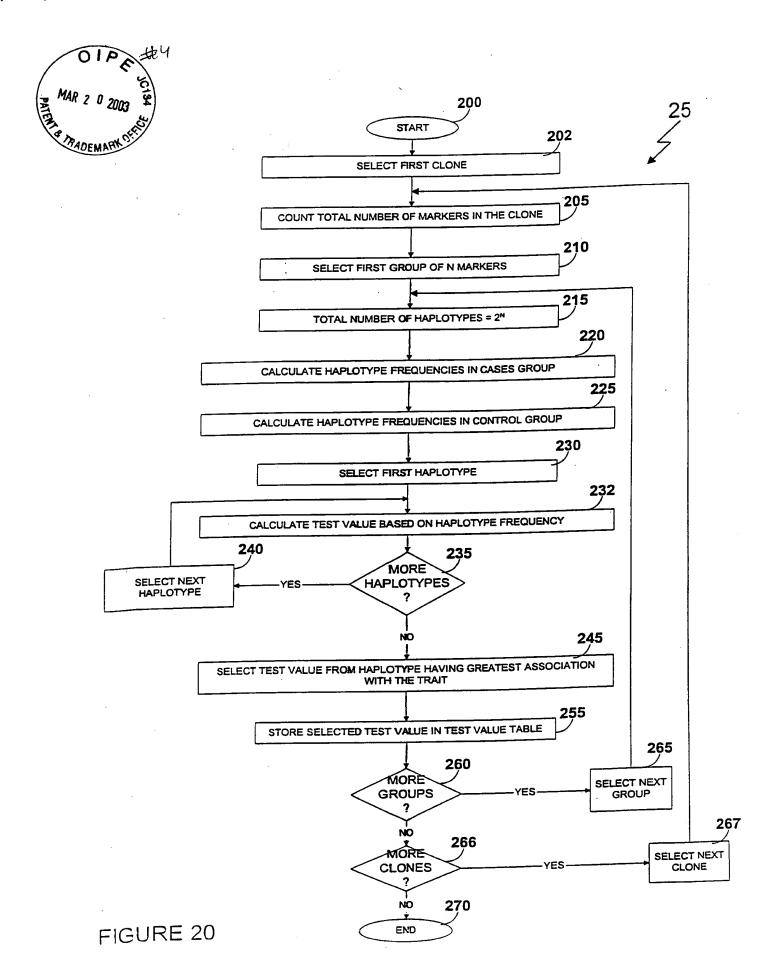
FIGURE 17 B



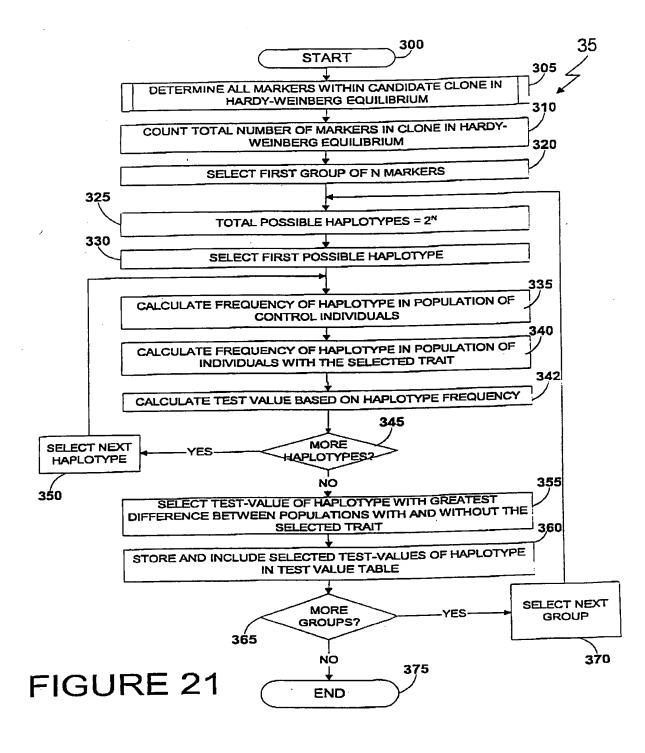














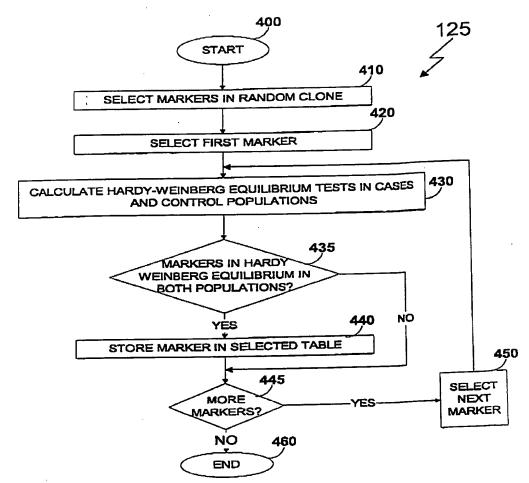


FIGURE 22



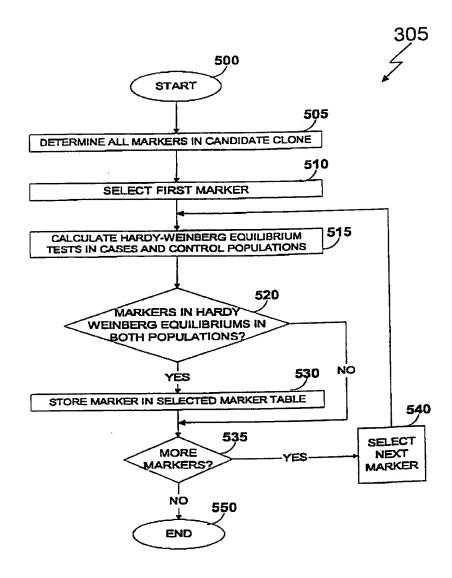


FIGURE 23



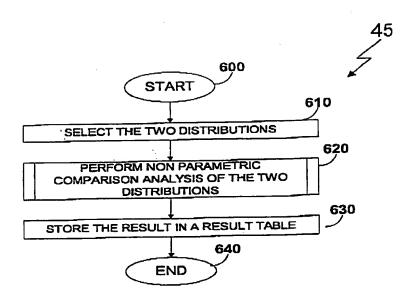


FIGURE 24



